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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/501,787	02/11/00	COEN	L 03495.0187

HM22/1005
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EXAMINER	
BRANNIDCE, M	
ART UNIT	PAPER NUMBER

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No. 09/501,787	Applicant(s) Coen et al.
Examiner Michael Brannock, Ph.D.	Art Unit 1646



— The MAILING DATE of this communication appears on the cover sheet with the correspondence address —

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on Aug 3, 2001

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle* 835 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-31 is/are pending in the application.

4a) Of the above, claim(s) 12-30 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1-11 and 31 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are objected to by the Examiner.

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) All b) Some* c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) Notice of References Cited (PTO-892)

18) Interview Summary (PTO-413) Paper No(s). _____

16) Notice of Draftsperson's Patent Drawing Review (PTO-948)

19) Notice of Informal Patent Application (PTO-152)

17) Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4

20) Other: _____

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Claim rejected under 35 U.S.C. 102() as being by .

DETAILED ACTION

Status of Application: Claims and Amendments

1. Applicant is notified that the amendments put forth in Paper 5 5/9/00 and in Paper 8, 8/3/01, have been entered in full.
2. Claims 1-31 are pending. Claims 12-30 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Further, claims 1-11 and will be examined only to the extent that the claims read on the in vivo delivery of a composition comprising fragment C of tetanus toxin plus at least 11 amino acids of fragment B. Further, claims 8-11 and 31 will be examined to the extent that they read on SMN protein. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

The traversal is on the grounds that a search of Groups I and II and/or of Groups I and III would not be a serious burden on the examiner. This is not found persuasive for the following reasons:

Under MPEP § 803, there are two criteria for a proper requirement for restriction between patentably distinct inventions:

(A) The inventions must be independent (see MPEP § 8702.01, 806.04, 808.01) **or** distinct as claimed (see MPEP § 806.05- §806.05(I)): and

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(B) There must be a serious burden on the examiner if restriction is required (see MPEP § 803.02, § 806.04(a)- 806.04(I), § 808.01(a), and § 808.02).

Consistent with current patent practice, a serious search burden may be established by (A) separate classification thereof: (B) a separate status in the art when they are classifiable together:

(C) a different field of search. These criteria were met in the above restriction. Further, a search is directed not only to art which would be anticipatory, but also to art that would render the invention obvious. In the instant case, although searches of the gene therapy of Group I and the polypeptides of Group III would overlap a search of the methods of administering a polypeptide of Group II, the three searches would not be coextensive, and to search all inventions would be burdensome. Additionally, Applicant's admission that the different species indicated as Groups A and B is noted. Thus, the different species will be examined upon the finding that the elected species is allowable. Therefore, the restriction is maintained and made final.

Priority

3. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

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Information Disclosure Statement

4. The information disclosure statement filed 5/9/00 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because no translation has been provided for EP 0030496. It has been placed in the application file, but the information referred to therein regarding EP 0030496 has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

Specification

5. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Rejections - 35 USC § 112

6. Claims 1-11 and 31 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards

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as the invention.

The claims require a proteolytic fragment of tetanus toxin in association with at least one molecule having a biological function. It is unclear what is meant by “in association with”. The specification at page 11 asserts that “in association means an association obtained by genetic recombination”. This definition does not appear to limit the phrase in any meaningful way. It is unclear what role genetic recombination plays in the obtainment of the association, i.e. does this definition strictly limit the method to fusion proteins (i.e. hybrid or chimeric proteins) as disclosed by Francis et al. J. Biol. Chem. 270(25)15343-15442, 1995, or does this definition also encompass the recombinant expression of the tetanus toxin C fragment (e.g. as disclosed by Fairweather et al., Infection and Immunity 55(11)2541-2545, 1997) followed by covalent conjugation of a second molecule (e.g. as disclosed by Fishman et al., J. Neurological Sciences 98(311-325)1990). Such a distinction cannot reasonably be made based on the guidance in the specification, however this distinction would certainly effect the bounds of the claims that Applicant is seeking protection for.

Additionally, the phrase “molecule having a biological function” renders the claims indefinite because the neither specification nor the claims define “biological function” such that the skilled artisan would unambiguously know what is encompassed by the claims. At page 10, the specification indicates that a molecule having a biological function is selected from the group consisting of [a] protein of interest (see lines 4-6); the specification then recites a series of examples of such proteins of interest. Examples, however, are insufficient to define the bounds

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of a claim. Since the invention appears to be directed to methods of delivering proteins of interest, it is suggested that the phrase “a protein of interested” replace the phrase “at least a molecule having a biological function” .

Similarity, the claims require “a protein for compensation or modulation of functions under the control of the CNS or the spinal cord or modulation of function in the CNS or the spinal chord”. The specification simply recites this phrase at page 10, however the specification does not define it. Thus, the specification does not provide the skilled artisan a definition of this phrase such that one skilled in the art can unambiguously know what is encompassed by the claims.

Claim 8 and dependent claims require “endonucleases like I-SceI” and diseases “such as latero spinal amyotrophy”. The words “like” and “such as” render the claims indefinite, because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 8 and dependent claims require a “protein SM”, there is no art recognized definition of this term and nor does the term appear in the specification. It appears that this maybe a minor typographical error, because the specification makes reference to the SMN protein (a.k.a NAIP), see page 10. Further, Applicants’ election of SMN protein (paper 8) will be considered for the purpose of this examination to encompass either of the proteins attributed in the specification (page 10) to Lefebvre (SMN1) or Roy (NAIP), however these proteins are known in the art to be distinct (see Liston et al. Nature 379(349)1996).

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Claim 31 requires the step of delivering the composition in a therapeutically effective manner, however the claim does not specify what in particular the therapy is effective for, therefore the metes and bounds of the claim cannot be determined.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims require that “said composition is capable of in vivo retrograde axonal transport”. Although it may not be Applicant’s intention, the claims require that the entire composition containing the protein be transported transsynaptically, i.e. the protein and any carrier/buffer or any other component of the composition be transported. There is no indication, either in the specification nor in the prior art, that this could happen.

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Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

10. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Boucher et al.,
Infection and Immunity 62(2)449-456, 1994.

Boucher et al. teach an in vivo method for delivery (i.p. injection, see page 450) of a composition (p75) comprising a nontoxic proteolytic fragment of tetanus toxin C fragment recombinantly fused to a second protein (pertussis toxin). Wherein said composition would be expected to be capable of in vivo retrograde axonal transport and transsynaptic transport in to the CNS, absent evidence to the contrary.

11. Claims 1-5 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No: 5780024.

U.S. Patent No: 5780024 discloses an in vivo method for delivery (e.g. intramuscular, see col 4) of a composition (SOD:Tet451), comprising a the tetanus toxin C fragment

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recombinantly fused to a second protein (e.g. SOD-1, see the Abstract), wherein said second protein is fused downstream to the tetanus toxin C fragment (see col 6) and wherein the fusion protein is capable of in vivo retrograde axonal transport and transsynaptic transport in to the CNS (e.g. from systemic administration to the brain stem, see col 1). Further, U.S. Patent No: 5780024 disclosed that the method can be used in the treatment of neurodegenerative diseases of the CNS (see col 1 for example).

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

13. Claims 6-8, 11 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5780024, as applied to claims 1-5 above, in view of Fairweather et al., Infection and Immunity 55(11)2541-2545, 1987.

U.S. Patent No: 5780024 discloses that the tetanus toxin C fragment used in the method of delivery can include additional amino acids, see col 6, as a matter of routine optimization of operating perimeters; yet U.S. Patent No: 5780024 does not disclose, specifically, that the C-fragment should contain at least 11 amino acids of the B-fragment. Fairweather disclose the

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recombinant use of the tetanus toxin C-fragment including at least 11 amino acids of the B-fragment (pTet18, see page 2541, 2nd col.) Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, with reasonable expectation of success to use a Tet C fragment with at least 11 amino acids of the B-fragment (as taught by Fairweather) when practicing the method taught by U.S. Patent No: 5780024. The motivation to do so was provided by both U.S. Patent No: 5780024, wherein it was taught that additional amino acids may be added to the C-fragment as a matter of routine optimization, and Fairweather et al. who taught that the C-fragment with additional amino acids of the B-fragment (pTet18) was more easy to obtain than that of the protein containing only the C-fragment (pTet11), see pg 253, last paragraph.

14. Claims 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5780024 in view of Fairweather et al., Infection and Immunity 55(11)2541-2545, 1987, as applied to claims 6-8, 11 and 31, above, and in further view of Fishman et al., J. Neurological Sciences 98(311-325)1990.

Claims 9 and 10 require a method as claimed in claims 6-8 as discussed above, yet claims 9 and 10 also require that the composition comprise at least two of said second molecules (claim 9) or that the said second molecule be located upstream of the tetanus toxin fragment. Fishman et al. teach that a second biologically active molecule can be conjugated to the tetanus C-fragment multiple times throughout the length (upstream or downstream) of the C-fragment

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(see page 313, middle paragraph and Figure 1, lanes 2 and 3). Therefore, it would be an obvious matter of routine optimization of operation parameters to incorporate at least two biologically active molecules to the C-fragment of the tetanus toxin, wherein at least one was associated upstream of the C-fragment, as taught by Fishman et al. when practicing the method of U.S. Patent No: 5780024 with modifications as taught by Fairweather et al. as discussed above. The motivation to do so is provided by Fishman et al. who teach that multimeric complexes are desirable (page 13 middle paragraph). Fishman et al., also provide the artisan with a reasonable expectation of success because Fishman et al. teach that the large size of such complexes does not interfere with the uptake of the complexes into neurons (page 322, middle paragraph).

15. Claims 6-8, 11 and 31 are also rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5780024 in view of Fairweather et al., Infection and Immunity 55(11)2541-2545, 1987, as applied to 6-8 , above, and in further view of U.S. Patent No: 6159948.

Applicant's elected species of SMN (claim 8) is not taught by either U.S. Patent No: 5780024 or Fairweather et al, as discussed above, however U.S. Patent No: 6159948 teaches the treatment of neurodegenerative disorders (e.g. spinal muscular atrophy, col 1) comprising the administration of the SMN protein (a.k.a NAIP) wherein the SMN protein is a fused to tetanus toxin or a fragment thereof (see col 21, last paragraph). Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, with reasonable expectation

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of success to modify the C-fragment of tetanus toxin as taught by Fairweather and by U.S. Patent No: 5780024, as discussed above, with the SMN protein as taught by U.S. Patent No: 6159948, for use in a method to deliver the SMN protein to the central nervous system. The motivation to do so was provided by U.S. Patent No: 6159948 wherein it is stated that increased levels of SMN protein (NAIP) can provide neuroprotection against neurodegenerative diseases (see the Abstract, and col 1), wherein the SMN protein should be fused to tetanus toxin or a fragment thereof (see col 21, last paragraph).

16. Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Francis et al. J. Biol. Chem. 270(25)15434-15442, 1995

Francis et al. disclose an in vitro method for delivery of a composition (SOD:Tet451), comprising a tetanus toxin C fragment recombinantly fused to a second protein (e.g. SOD-1, see the Abstract), wherein said second protein is fused downstream to the tetanus toxin C fragment (see col 6) and wherein, absent evidence to the contrary, the fusion protein is capable of in vivo retrograde axonal transport and transsynaptic transport in to the CNS (e.g. from systemic administration to the brain stem, see page 15434). Francis et al. did not use the method for in vivo delivery, however they proposed to do so (see the Abstract, for example). Further, Francis et al disclosed that the method could be used in the treatment of neurodegenerative diseases of the CNS (15434 see col 1 for example). Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made to with reasonable expectation of

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success to use the in vitro method of delivery disclosed by Francis et al. for in vivo delivery, as required by the instant claims. The motivation to do so was provided by Francis et al. who state the tetanus toxin has a well documented capacity for neuronal binding and internalization. In particular when administered systemically or intramuscularly to animals, the toxin is taken up selectively by motor neurons in the brain stem and spinal chord. The C-fragment retains these properties without the toxic domain (see 15434 see col 1). Further, Francis et al. hypothesize that their disclosed fusion protein could increase the delivery of the SOD-1 protein to the central nervous system in general and motor neurons in particular, potentially providing effective enzyme therapy to neurons (see 15434 see col 1).

17. Claims 6-8, 11 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Francis et al. J. Biol. Chem. 270(25)15434-15442, 1995, as applied to claims 1-5 above, in view of Fairweather et al., Infection and Immunity 55(11)2541-2545, 1987.

Francis et al. disclose that it is the C-fragment of tetanus that provides for neuronal binding and internalization without toxicity, yet Francis et al. do not disclose, specifically that the C-fragment should contain at least 11 amino acids of the B-fragment. Fairweather disclose the recombinant use of the tetanus toxin C-fragment including at least 11 amino acids of the B-fragment for in vivo delivery (pTet18, see page 2541, 2nd col.) Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made to, with reasonable expectation of success to use a Tet C fragment with at least 11 amino acids of the B-fragment (as

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taught by Fairweather) when practicing the method taught and proposed by Francis et al. The motivation to do so was provided by Fairweather et al. who taught that the C-fragment with additional amino acids of the B-fragment (pTet18) was more easy to obtain than the protein containing only the C-fragment (pTet11), see pg 253, last paragraph.

18. Claims 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Francis et al. J. Biol. Chem. 270(25)15434-15442, 1995 in view of Fairweather et al., Infection and Immunity 55(11)2541-2545, 1987, as applied to claims 6-8, 11 and 31, above, and in further view of Fishman et al., J. Neurological Sciences 98(311-325)1990.

Claims 9 and 10 require a method as claimed in claims 6-8 as discussed above, yet claims 9 and 10 also require that the composition comprise at least two of said second molecules (claim 9) or that the said second molecule be located upstream of the tetanus toxin fragment. Fishman et al. teach that a second biologically active molecule can be conjugated to the tetanus C-fragment multiple times throughout the length (upstream or downstream) of the C-fragment (see page 313, middle paragraph and Figure 1, lanes 2 and 3). Therefore, it would be an obvious matter of routine optimization of operation parameters to incorporate at least two biologically active molecules to the C-fragment of the tetanus toxin, wherein at least one was associated upstream of the C-fragment, as taught by Fishman et al. when practicing the method of Francis with modifications as taught by Fairweather et al. as discussed above. The motivation to do so is

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provided by Fishman et al. who teach that multimeric complexes are desirable (page 13 middle paragraph). Fishman et al., also provide the artisan with a reasonable expectation of success because Fishman et al. teach that the large size of such complexes does not interfere with the uptake of the complexes into the neurons (page 322, middle paragraph).

19. Claims 6-8, 11 and 31 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Francis et al. J. Biol. Chem. 270(25)15434-15442, 1995 in view of Fairweather et al., Infection and Immunity 55(11)2541-2545, 1987, as applied to 6-8 , above, and in further view of U.S. Patent No: 6159948.

Applicant's elected species of SMN (claim 8) is not taught by either Francis et al. or Fairweather et al, as discussed above, however U.S. Patent No: 6159948 teaches the treatment of neurodegenerative disorders (e.g. spinal muscular atrophy, col 1) comprising the administration of the SMN protein (a.k.a NAIP) wherein the the SMN protein is a fused to tetanus toxin or a fragment thereof (see col 21, last paragraph). Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, with reasonable expectation of success to modify the C-fragment of tetanus toxin as taught by Fairweather and by Francis et al., as discussed above, with the SMN protein as taught by U.S. Patent No: 6159948, for use in a method to deliver the SMN protein to the central nervous system. The motivation to do so was provided by U.S. Patent No: 6159948 wherein it is stated that increased levels of SMN protein (NAIP) can provide neuroprotection against neurodegenerative diseases (see the Abstract, and

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col 1), wherein the SMN protein should be fused to tetanus toxin or a fragment thereof (see col 21, last paragraph).

20. Claims 6-8, 11 and 31 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Francis et al. J. Biol. Chem. 270(25)15434-15442, 1995 in view of Fairweather et al., Infection and Immunity 55(11)2541-2545, 1987, as applied to 6-8 , above, and in further view of Liston et al., Nature 379(6563)349-53.

Francis et al., teach that SOD-1 can be used as a fusion partner of tetanus toxin C fragment for delivery into neuronal cells for the protection against free radical induced neurological disorders (see the first paragraph); however applicant's elected species of SMN (a.k.a NAIP) (claim 8) is not taught by either Francis et al. or Fairweather et al, as discussed above. Liston et al. teach that the NIAP protein can protect cells against apoptosis induced by a variety of signals, including those that underlie certain neurodegenerative disorders, e.g. spinal muscular atrophy (see the Abstract). Such signals resulting from free radical induced apoptosis (see col 2 of pg 349). Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, with reasonable expectation of success to modify the C- fragment of tetanus toxin as taught by Fairweather and by Francis et al., as discussed above, with the NAIP protein as taught by Liston et al., for use in a method to deliver the NAIP protein to the central nervous system. The motivation to do so was provided by Liston et al. teach that the

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NIAP protein can protect cells against apoptosis induced by a variety of signals, including those that underlie certain neurodegenerative disorders, e.g. spinal muscular atrophy (see the Abstract).

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Yvonne Eyler
YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
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October 3, 2001